UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge Oral Argument Requested

DEFENDANTS' MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT GEORGE JOHNSON, PH.D.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Other Authorities

Pursuant to Federal Rules of Evidence 104, 403, and 702, Defendants' Executive Committee, on behalf of all Defendants in this litigation, submit this Memorandum of Law in Opposition to Plaintiffs' Motion to Preclude Opinions of Defense Expert George Johnson, Ph.D. ("Opposition").[1]

INTRODUCTION

The scientific question before the Court is whether the additional exposure to trace levels of NDMA and NDEA found in certain valsartan batches causes an increased risk of cancer in the patients taking the medication prior to the recall. The exposure is "additional" because each of us are exposed on a daily basis to levels of NDMA and NDEA in our diet and through endogenous production. Dr. Johnson explains how and why the additional micrograms of NDMA from the valsartan do not create additional risk because of the body's DNA repair process. His opinion is based upon an actual peer reviewed study that determined a Permissible Daily Exposure level ("PDE") for NDMA and NDEA, and when the calculation is applied to the plaintiff population at hand, the levels of NDMA and NDEA reported in the valsartan are within the Permissible Daily Exposure level. Dr. Johnson's opinions and methodology have been peer reviewed and published in the seminal article on this issue.

[1] A copy of Defendants' Rule 26 Disclosure of Expert Witnesses for General Causation, served August 2, 2021, is attached as **Exhibit A**.

Dr. Johnson's expert report in this caseused the same methodology and merely refocused his calculations from his 2021 article to the relevant patient population here based on Plaintiffs' reported body weight, and he demonstrates that in 100 kg people the body can withstand an additional measure of exposure and maintain a complete defense to the NDMA mutations, when the confidence interval and upper limit is applied. This range encompasses the daily exposure Plaintiffs could reasonably have had over the relevant timeframe. Importantly Plaintiffs have introduced no evidence or expert opinion that is contrary to this PDE, so they put misplaced reliance on FDA's AI calculation and ask the Court to ignore the science clearly demonstrating low-level exposure tolerance, i.e. no increased risk. Dr. Johnson's opinions regarding the cellular response to NDMA, the mutation and DNA repair process that is not disputed, will most certainly aid the trier of fact in this case.

Plaintiffs' Motion to Preclude Opinions of Defense Expert George Johnson, Ph.D. ("Motion") is predicated on Plaintiffs' misguided attempt to reframe the general causation question in this litigation as though causation can be established merely by determining whether the NDMA and/or NDEA compounds found in the valsartan medications exceeded the FDA's Acceptable Intake ("AI") calculation. Even FDA does not contend the AI they calculated represents a general causation threshold, and acknowledged at the FDA Nitrosamine Workshop in March 2021 that

their AI may be meaningless if the body produces magnitudes greater of NDMA endogenously.[2]

The actual question of general causation before this Court is whether Plaintiffs have carried their burden of proving that NDMA and/or NDEA are carcinogenic to humans at the levels detected in the subject batches of valsartan during the alleged period of potential exposure. *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1242 (5th Cir. 2005) (citing *Science for Judges I: Papers on Toxicology and Epidemiology* 12 J. L. & Pol'y. 1 (2003): "Dose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect. Often low dose exposures -- even for many years -- will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage. Furthermore, for most types of dose-response relationships following chronic (repeated) exposure, thresholds exist, such that there is some dose below which even repeated, long-term exposure would not cause an effect in any individual"); *In re Abilify (Aripiprazole) Prods. Liab. Litig.,* 299 F. Supp. 3d 1291, 1307-08 (N.D. Fl. 2018) ("for the vast majority of substances, there are threshold doses below which no individual will respond… Consequently, a reliable expert

[2] FDA, Nitrosamine Workshop – Report Final, at 14 (July 20, 2021), *available at* https://www.fda.gov/media/150932/download (last visited November 29, 2021) (attached as **Exhibit B**).

opinion on general causation should address what levels of exposure to a drug increase the risk of adverse effects. Indeed, the expert who avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology"); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, (N.D. Cal. 2007) (excluding expert opinions that medication could cause claimed harm at lower doses than studied). This is the precise question Dr. Johnson answers here and in his peer-reviewed publication that determined the PDE for NDMA and NDEA.[3]

Plaintiffs' Motion raises a series of ill-connected challenges primarily attacking Dr. Johnson's methodology. Plaintiffs create a series of strawmen only to knock them over. They make no claim that he is not qualified to offer the opinions rendered or argue that his opinions do not fit the litigation. None of the particular arguments raised merits excluding or limiting Dr. Johnson's opinions in any fashion.

Plaintiffs challenge Dr. Johnson's PDE limits for NDMA and NDEA which were calculated using FDA-approved benchmark dose methodology. Plaintiffs' desire to rely on the FDA's AI calculation as a proxy for general causation demonstrates their refusal to confront the true general causation question which must

[3] Johnson GE, Dobo K, Gollapudi B, Harvey J, Kenny J, Kenyon M, Lynch A, Minocherhomji S, Nicolette J, Thybaud V, Wheeldon R, Zeller A, *Permitted daily exposure limits for noteworthy N-nitrosamines*, ENVIRON. MOL. MUTAGEN. 62(5):293-305 (2021) ("Johnson 2021") (attached as **Exhibit C**).

consider the metabolism of NDMA and the DNA repair process associated with NDMA mutations which defends against the mechanism of carcinogenicity from NDMA. Dr. Johnson's PDE calculations utilize the benchmark dose ("BMD" or "BMDL") methodology specifically approved by the FDA's guidance on nitrosamines and in the ICH M7(R)(1). The PDE calculation by Dr. Johnson directly addresses the question of whether the incremental increased exposure from low levels of impurities found in some valsartan medication poses a risk to humans, whereas the FDA's AI calculation is less precise, ignores human factors, is intentionally overly conservative, and serves a different and, as it relates to the general causation determination, largely irrelevant purpose.

Plaintiffs further claim, again incorrectly, that NDMA and NDEA are "no threshold" carcinogens, by pointing to the *Peto* study. However, the *Peto* study did not attempt to identify a threshold as Dr. Peto acknowledged in the article.[4] The *Peto* data has subsequently been shown to demonstrate there is a threshold, and a non-linear dose response at low levels. Plaintiffs' argument shows an alarming ignorance of the underlying evidence.

Plaintiffs' argument that Dr. Johnson's opinions are litigation-driven and do

[4] Peto, R et al., *Effects on 4080 Rats of Chronic Ingestion of Nitrosodiethylamine or N-Nitrosodimethylamine: A detailed dose response study*, CANCER RESEARCH 51:6415-6451, 6445 (1991) (attached as **Exhibit D**).

not grow naturally out of his existing work and scholarship is equally specious. Dr. Johnson has spent his nearly two decades in research and academia analyzing the impact of low levels of mutagenic compounds on humans, the DNA repair process, and risk of carcinogenicity. Dr. Johnson has published multiple studies in peer-reviewed journals where he determined PDE levels in other mutagenic compounds.[5] More than any other expert in this litigation, Dr. Johnson's entire body of work prepared him to address the particular questions in this litigation, as evidenced by the fact he was sought after by global regulatory agencies to present on this topic prior to being engaged as an expert and was working on his now-seminal paper addressing N-nitrosamine impurities *before* he ever became involved in this litigation.

Plaintiffs' argument that Dr. Johnson's report contains "theoretical and conceptual assumptions" and is therefore not reliable misinterprets and/or ignores the applicable law and relevant science. Dr. Johnson's methodology for deriving the PDE in both his published work and specifically for purposes of evaluating general

[5] *See, e.g.*, Macgregor, James T, et al., *IWGT report on quantitative approaches to genotoxicity risk assessment I. Methods and metrics for defining exposure–response relationships and points of departure (PoDs)*, MUTATION RESEARCH, 783:55-65 (2015) (attached as **Exhibit E**); G.E. Johnson, et al., *Derivation of Point of Departure (PoD) Estimates in Genetic Toxicology Studies and Their Potential Applications in Risk Assessment*, ENVIRON. MOL. MUTAGEN. 55:609-623 (2014) (attached as **Exhibit F**).

causation in this litigation are based on peer-reviewed literature and well-established science.

Plaintiffs repeatedly misrepresent Dr. Johnson's testimony on his PDE calculation in a transparent attempt to mischaracterize the underlying methods and calculations as novel or not generally accepted in the wider scientific community. However, the underlying methods and concepts which led to the PDE limits as stated in Dr. Johnson's expert report are merely the first peer-reviewed application of well-established scientific principles and methodology to the particular compounds at issue. The decision of FDA and other regulatory agencies to set their AI levels using the conservative TD50 linear back-extrapolation method demonstrates only that these regulators operate as conservatively as possible and were not attempting to answer the general causation question at issue in this litigation. Adopting the FDA's AI as a general causation threshold here would result in creating a scientific falsity, and Dr. Johnson's opinions explain why the AI cannot be construed as meaning that levels above the AI cause cancer.

Plaintiffs' Motion makes several passing allegations of bias with respect to Dr. Johnson due to his work on studies and publications in partnership with various pharmaceutical companies. This claim ignores the extensive work that Dr. Johnson has done on behalf of regulatory agencies as a renowned expert in this area, plus his highly regarded work at his own academic institution. Not only is Plaintiffs'

argument without merit, these issues would only serve as a basis for cross-examination, not exclusion of his testimony or opinions.

The argument that Dr. Johnson "cherry-picked" his data by basing his calculations on the levels reported by the FDA inverts the cherry-picking inquiry. It is Plaintiffs who attempt to ignore the most reliable, relevant testing data (which is the data reported by FDA, as explained by Dr. Johnson during his deposition), and instead argue that Dr. Johnson should have selectively relied on the highest outlier numbers from internal testing data, without regard to the consistency of testing methods used, whether that product was representative of the manufacturer's finished dose product as a whole, or whether the testing was performed on valsartan finished dose or valsartan API.

Plaintiffs' final attack on Dr. Johnson argues that he, as a genetic toxicologist, should have analyzed and relied on dietary and occupational studies in forming his general causation opinions. This argument belies a misunderstanding of Dr. Johnson's opinions, the field of toxicology, or both, which is perhaps unsurprising given that Plaintiffs failed to proffer expert opinions from any toxicologist to support their theories in this litigation. The referenced dietary and occupational studies are at best the basis for an epidemiologist to review and begin to determine if an association or causal association exists – they are not relevant to Dr. Johnson's toxicology analysis beyond providing general background on other

potential sources of nitrosamines.

In sum, Plaintiffs' Motion contains scattershot arguments that do not undermine Dr. Johnson's robust and well-documented methodology, and Plaintiffs do not even challenge Dr. Johnson's extensive qualifications or that his opinions fit the facts of this litigation. For these reasons, as stated more fully below, Plaintiffs' Motion should be denied.

LEGAL STANDARD

Federal Rule of Evidence 702[6] provides that a witness who is "qualified as an expert by knowledge, skill, experience, training, or education" may offer opinions in a case if (i) the expert's "scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue"; (ii) "the testimony is based on sufficient facts or data"; (iii) "the testimony is the product of reliable principles and methods"; and (iv) "the expert has reliably applied the principles and methods to the facts of the case." The Third Circuit has explained that Rule 702 "provides for 'a trilogy of restrictions on expert testimony: qualification,

[6] On August 6, 2021, the Judicial Conference Committee on Rules of Practice and Procedure approved the publication of a proposed amendment to Rule 702 for public comment. *See* Judicial Conference of the United States, "Preliminary Draft Proposed Amendments to the Federal Rules of Appellate, Bankruptcy, Civil, and Criminal Procedure, and the Federal Rules of Evidence" (August 2021), *available at* https://www.uscourts.gov/sites/default/files/preliminary_draft_of_proposed_amendments_2021_0.pdf.

reliability, and fit.'" *R.D. v. Shohola, Inc.*, 2019 WL 6053223, at *3 (M.D. Pa. Nov. 15, 2019) (quoting *Calhoun v. Yamaha Motor Corp.*, 350 F.3d 316, 321 (3d Cir. 2003)). Under Rule 702, the trial judge acts as a "gatekeeper" to ensure that before it is presented to a jury, expert testimony is "both relevant and reliable." *Id* . (quoting *Buzzerd v. Flagship Carwash of Port St. Lucie, Inc.*, 669 F. Supp. 2d 514, 519 (M.D. Pa. 2009) (citing *Daubert*, 509 U.S. at 589)). In cases where a party objects to the admissibility to proffered expert opinion testimony, the court must examine qualifications, reliability, and fit. *Id.* (citing *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 741-47 (3d Cir. 1994) ("*Paoli II*")). In other words, a qualified expert's "testimony must [(1)] be based on sufficient facts and data; (2) must be the product of a reliable methodology; and (3) must demonstrate a relevant connection between that methodology and the facts of the case." *Id.* (quoting *Jaasma v. Shell Oil Co.*, 412 F.3d 501, 513 (3d Cir. 2005)).

The proper test for reliability is whether the particular opinion is based on valid reasoning and reliable methodology. *Id.* (citing *Kannankeril v. Terminix Int'l*, 128 F.3d 802, 806 (1997)). In determining whether proposed testimony is sufficiently reliable, courts are to consider the following factors: (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the

method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put. *Id.* (citing *In re Paoli R.R. Yard Pcb Litig.*, 35 F.3d 717, 742 n.8 (3d Cir. 1994)).

Scientific disagreement is not sufficient grounds for the exclusion of expert testimony and is not for the Court to decide in its capacity as a gatekeeper under Rule 702/*Daubert*. *See, e.g., In re Gabapentin Patent Litig.*, MDL Dkt. No. 1384, 2011 WL 12516763, at *10 (D.N.J. Apr. 8, 2011) (concluding that disagreement between experts regarding application of a methodology presents "a battle of the experts" to be resolved by the trier of fact); *United States v. W.R. Grace*, 455 F. Supp. 2d 1196, 1199 (D. Mt. 2006) (Expert testimony even as to disputed evidence is admissible under Rule 702: "It appears that there is some scientific disagreement . . . . It is not the Court's role to settle scientific disputes . . . it is an issue going to the weight of the evidence, and is best left to the jury"); *see also Broe v. Manns*, No. 15-985, 2016 WL 7048988, at *4 (M.D. Pa. Dec. 5, 2016) ("Any disagreement plaintiffs have with the expert can be dealt with through cross-examination, presentation of contrary evidence and proper jury instructions"); *In re Asbestos Prods. Liab. Litig.*, 714 F. Supp. 2d 535, 544 (E.D. Pa. 2010); *In re Diet Drugs Prods. Liab. Litig.,* MDL No. 1203, 2000 WL 962545, at *13 (E.D. Pa. June

28, 2000) (finding that disagreement with the methods used by an expert is a question that "goes more to the weight of the evidence than to reliability for Daubert purposes").

As set forth below, Dr. Johnson's opinions satisfy all the requirements of Rule 702 and Plaintiffs have not offered any cognizable grounds for excluding those opinions.

ARGUMENT

I. PLAINTIFFS DO NOT CHALLENGE DR. JOHNSON'S QUALIFICATIONS OR ARGUE THAT HIS OPINIONS DO NOT "FIT" THIS LITIGATION.

There are three grounds for excluding an expert witness's testimony under Rule 702 – qualifications, methodological reliability, and fit. Fed. R. Evid. 702; *Yarchak v. Trek Bicycle Corp.*, 208 F. Supp. 2d 470, 496 (D. NJ. 2002); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 595 (D.N.J. 2002), *aff'd*, No. 02-2331, 2003 WL 21467223 (3rd Cir. June 25, 2003).

As a preliminary matter, Plaintiffs do not argue that Dr. Johnson is not qualified to offer the opinions set forth in his report. (*See generally* Plaintiffs' Motion). Nor do they argue that Dr. Johnson's opinions do not "fit" this litigation, as it most clearly does. (*See generally id.*). Rather, the scattershot series of complaints Plaintiffs raise with respect to Dr. Johnson all purport to relate to his methodology and whether said methodology is reliable. (*See id.* at 9-29). Defendants

respond below to each of these arguments in turn.

II. DR. JOHNSON'S OPINIONS ARE THE RESULT OF RELIABLE METHODOLOGY WHICH HE APPLIES TO ADDRESS THE GENERAL CAUSATION QUESTION IN THIS LITIGATION.

Dr. Johnson reached his conclusions after applying the Benchmark Dose Methodology[7] to the available testing data for the valsartan manufacturers. Dr. Johnson reasonably chose to rely on the levels reported by the FDA, which had the best access to the manufacturers' finished dose product actually sold or intended for sale in the United States and was able to conduct uniform testing of the finished dose products to calculate these levels. The methodology employed by Dr. Johnson is not "his" but rather a widely accepted method by the scientific community that considers human factors when extrapolating from animal studies. Contrary to Plaintiffs' repeated misstatements, the methodology is specifically authorized within the ICH M7 guidelines for assessing pharmaceutical impurities and is accepted by

[7] *See* ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017), Note 4 (attached as **Exhibit G**). ("[I]n order to better take into account directly the shape of the dose-response curve, a benchmark dose such as a Benchmark Dose Lower Confidence Limit 10% (BMDL10, an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents) may be used instead of TD50 values as a numerical index for carcinogenic potency.").

all the relevant regulatory bodies cited by Plaintiffs.[8]

A. NDMA and NDEA display a threshold mechanism and are therefore appropriately assessed using the benchmark dose methodology for calculation of a PDE.

Dr. Johnson calculated a PDE for both NDMA and NDEA based upon data that unequivocally establishes a non-linear lose-dose threshold for both mutagenicity and carcinogenicity of NDMA and NDEA. Dr. Johnson's results from use of this methodology were completed and peer reviewed prior to preparing the report in this case. As stated in his report and repeated throughout his deposition, these calculations demonstrate the levels of exposure below which Dr. Johnson can say conclusively that there is no increased risk of cancer in humans from exposure to NDMA and/or NDEA due to DNA repair, cancer bioassay data, and human biology. (*See, e.g.*, George Johnson Depo. Trans., Oct. 5, 2021, attached as **Exhibit I**, 396:18 – 397:6; *see also* Johnson 2021, *supra* (attached as **Exhibit C**)). The BMD approach is discussed extensively in the ICH M7 guidelines adopted by FDA in its Guidance on Nitrosamines, and the PDE calculation using the BMD approach employed by Dr. Johnson is similarly well-established. PDE determinations by Dr. Johnson and others using the BMD approach have been published in peer reviewed journals since

[8] *See, e.g.*, FDA, M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (March 2018), (attached as **Exhibit H**).

at least 2015.[9] Plaintiffs first attempt to claim that these widely accepted methodologies are suspect because the threshold mechanism for NDMA and NDEA is "left undefined." (Motion at 9). Dr. Johnson does not leave the threshold "undefined," as Plaintiffs' allege – he discusses the observed threshold extensively as part of his explanation of his PDE calculation and he included a chart illustrating the threshold in his report. (*See* Motion at 9; Expert Report of George E. Johnson, dated August 2, 2021, at 42 (attached as **Exhibit J**) ("Johnson Report").

Plaintiffs' primary disagreement with Dr. Johnson's PDE is that it differs from the AI calculated by the FDA. They allege a number of so-called "concessions" on this topic where Dr. Johnson simply acknowledges that the FDA used the TD50 linear back extrapolation method to calculate the AI for NDMA and NDEA. (*See* Motion at 9-11). But Plaintiffs omit Dr. Johnson's opinion and testimony that this TD50 method used by FDA is not a reliable determination of actual human risk.[10]

Plaintiffs presume to divine the FDA's and EMA's intent as based on "the lack of sufficient data and scientific recognition" by citing an EMA Assessment Report which neither contains any information on the FDA's decision-making process nor rejects the BMDL method due to anything approaching the conclusory

[9] *See, e.g.*, Macgregor, *supra* note 5 (attached as **Exhibit E**); G.E. Johnson, *supra* note 5 (attached as **Exhibit F**).

[10] *See* Johnson Report at 44-48; *see, e.g.*, **Exhibit I**, 348:7-349:13.

language used by Plaintiffs. (*See* Motion Exh. E at 43-44). Moreover, this very document cited by Plaintiffs supports Dr. Johnson's factual testimony on the conservative, regulatory nature and purpose of the TD50: "The linear extrapolation framework is a conservative/precautionary regulatory risk assessment approach for genotoxic carcinogens . . . ." (*Id.* at 43). The EMA also acknowledges that in the TD50 "[t]here are no adjustment factors for extrapolation from animal to humans." (*Id.* at 44).

The FDA's AI limit is a regulatory decision motivated by conservative, regulatory goals. Numerous courts have recognized that such determinations are not equivalent to a general causation analysis in the context of litigation. "The FDA will remove drugs from the marketplace upon a lesser showing of harm to the public than the preponderance-of-the-evidence or more-likely-than-not standards used to assess tort liability." *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001). "The methodology employed by a government agency 'results from the preventive perspective that the agencies adopt in order to reduce public exposure to harmful substances.'" *Id.* (citing *Hollander v. Sandoz Pharms. Corp.*, 95 F.Supp.2d 1230, 1234 n. 9 (W.D. Okla. 2000)). Applying these principles in the context of medical causation in personal injury actions, courts have consistently concluded that "recommended or prescribed precautionary standards cannot prove legal causation . . . . **Failure to meet regulatory standards is simply not sufficient to**

establish general causation." *Mancuso v. Consol. Edison Co.*, 967 F. Supp. 1437, 1448 (S.D.N.Y. 1997) (quoting *In re Agent Orange Prod. Liab. Litig.*, 597 F. Supp. 740, 781 (E.D.N.Y. 1984) (emphasis added)); *see also Mitchell v. Gencorp, Inc.*, 165 F.3d 778, 783 n.3 (10th Cir. 1999); *Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194, 198 (5th Cir. 1996) (observing "the fact that EtO has been classified as a carcinogen by agencies responsible for public health regulations is not probative of the question whether Allen's brain cancer was caused by EtO exposure.").

The dispute over whether the TD50 or BMDL with a PDE method is better suited to assist the trier of fact in assessing general causation is, at best, an issue to explore on cross-examination, and does not serve as a basis to exclude or limit Dr. Johnson's testimony in this area.

B. Plaintiffs mischaracterize the conclusions of the *Peto* study, which provided the data on NDMA and NDEA to support the threshold analysis Dr. Johnson carried out in his peer reviewed article and in this case.

Dr. Johnson cites to and relies on the *Peto* study data in support of his opinion there is a non-linear threshold of carcinogenicity risk at low doses of NDMA and NDEA.[11] However, Plaintiffs misrepresent and mischaracterize the *Peto* study results and the author's[12] carefully worded conclusions, which specifically declined

[11] Peto, *supra* note 4 (attached as **Exhibit D**).

[12] It is important to note the author, Dr. Peto, was a statistician, not a toxicologist, and in the absence of calculations of the dose-response at low-doses, the author

to try to identify and characterize a threshold response: "There has been no attempt in the present report to connect the low-dose dose response relationship with the high-dose dose response relationship . . . ."[13] Rather, *Peto* noted the presence of "artifacts" in the linear model and invited precisely the type of analysis performed by Dr. Johnson, who reviewed the extensive database and determined: "Both the NDMA and NDEA in the Peto study showed a dose response in the cancer bioassay for both substances." (**Exhibit I**, 352:3-5). Dr. Johnson's conclusion is supported by peer-reviewed literature published after *Peto* which similarly looked at the dataset and demonstrated that the data showed a clear threshold for both substances.[14]

In sum, Plaintiffs misinterpret the language in *Peto* which found no threshold within the low-dose and high-dose groups, but made no attempt to quantify or assess the dose-response relationship between these groups. Dr. Johnson, on the other hand, calculated the threshold for NDMA and NDEA using the very data *Peto* provided.[15]

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admits it is speculation and he believes the data will reveal a threshold just as Dr. Johnson and others have done. *See* Marco J. Zeilmaker, Martine I. Bakker, Ronald Schothorst, Wout Slob, *Risk Assessment of N-nitrosodimethylamine Formed Endogenously after Fish-with-Vegetable Meals*, TOXICOLOGICAL SCIENCES, Volume 116, Issue 1, Pages 323–335 (2010) (attached as **Exhibit K**).

[13] Peto, R, *supra* note 4, at 6445 (attached as **Exhibit D**).

[14] *See* Zeilmaker, *supra* note 12 (attached as **Exhibit K**).

[15] *See* Johnson 2021, *supra* (attached as **Exhibit C**).

C. Dr. Johnson's opinions grow naturally from his extensive body of research analyzing the impact of low levels of mutagenic compounds on humans and his work on calculating the PDEs for NDMA and NDEA which started in 2018.

Dr. Johnson's body of genotoxic impurities research involves the assessment of low levels of exposure to such compounds on both animal and human tissue, focusing on the DNA mutation and repair process. (*See* Johnson Report at 2-3). He has specifically employed the benchmark dose approach (BMDL) and calculated PDEs for various impurities. (*Id.* at 2; Dr. George Johnson CV, Exh. A to Johnson Report, at 4-8 (attached as **Exhibit L**)). This research dates back to at least 2005.[16] The very reason Dr. Johnson was identified to assist with this litigation was that in June of 2018 he was already presenting to global regulatory bodies on precisely these issues. (George Johnson Depo. Trans., Oct. 4, 2021, attached as **Exhibit M**, 53:16 – 55:11). Before he was even engaged for this litigation he was calculating the PDEs for NDMA and NDEA that form the basis of his now-seminal paper applying these scientific principles and methodology to NDMA and NDEA. (*Id.*, 154:9 – 157:13).

The claim that his work in this litigation does not grow out of his existing body of research could not be more untrue. Dr. Johnson was at the forefront of this issue, including publishing the first peer-reviewed analysis specifically assessing

[16] Jenkins GJ, Doak SH, Johnson GE, Quick E, Waters EM, Parry JM., *Do dose response thresholds exist for genotoxic alkylating agents?*, MUTAGENESIS 20(6):389-398 (2005) (attached as **Exhibit N**).

these compounds.[17] That his earlier work in this area did not specifically assess NDMA and/or NDEA is of no moment – the methodology is the same. Plaintiffs' claim that his research and opinions should somehow be subject to a higher level of "scrutiny" based on these facts strains credulity, but regardless does not serve as a basis for excluding or limiting any of his opinions under Rule 702.

D. Dr. Johnson follows established methodologies in forming his opinions.

Plaintiffs' argument that Dr. Johnson's report contains "theoretical and conceptual assumptions" and is therefore not reliable misinterprets the applicable law and relevant science. Dr. Johnson's methodology for deriving the PDE in both his published work and specifically for purposes of evaluating general causation in this litigation are based on peer-reviewed literature.[18] The fact that Dr. Johnson, the world's foremost expert in this area, cites to his and his highly-qualified colleagues' own work in this area does not render his opinions any less reliable.

Plaintiffs further take issue with Dr. Johnson's calculations pertinent to a 100 kg valsartan patient. The 50 kg calculations used in Dr. Johnson's paper illustrate the baseline levels of exposure to which his PDE could apply for any theoretical human, just as FDA's AI uses a fictional (or "theoretical") 50 kg human

[17] *See* Johnson 2021, *supra* (attached as **Exhibit C**).

[18] *See, e.g.*, Johnson 2021, *supra* (attached as **Exhibit C**); Macgregor, *supra* n.4 (attached as **Exhibit E**); Johnson, *supra* n.4 (attached as **Exhibit F**);

in their AI calculation. Notably, the FDA also applies a 70-year exposure period to the AI calculation,[19] which makes no sense from a general causation standpoint and is not based on the reality of the Plaintiffs in this litigation or the patient population at issue. Dr. Johnson did not "stealthily" introduce the 100 kg calculation[20] – he used this number based on a statistical analysis of the actual bellwether Plaintiff pool in this MDL, which provides a much more accurate estimate of the true patient population. As Dr. Johnson explained: "I adjusted this to the more realistic average population of 100 kilograms for the individuals here. As I would see from average population size, 100 would be closer to the population average, in this case. So I did that calculation in my report." (**Exhibit I**, 377:13-19). These weights are consistent with the weights published by the Center for Disease Control and Prevention ("CDC") which Dr. Johnson considered in evaluating the appropriate weights for purposes of his analysis.[21] The differing weights used in his published paper (prepared for general peer-review and public consumption) and his report in this case (prepared to address the specific general causation inquiry before the Court) is not an inconsistency and the basis for the numbers is clearly delineated in Dr. Johnson's

[19] **Exhibit I**, 354:17-24.

[20] Motion at 14.

[21] **Exhibit I**, 479:23-480:8; National Center for Health Statistics, "Anthropometric Reference Data for Children and Adults: United States, 2015–2018" (January 2021) (attached as **Exhibit Q**).

report and testimony.[22] That the FDA's simplistic AI calculation makes no adjustment for weight – or human DNA repair or biology – has no bearing on the relevance of weight to Dr. Johnson's PDE.

Plaintiffs then resort to mischaracterizing Dr. Johnson's own testimony, in which he acknowledges that the calculations in his report are not identical to those in his 2021 paper, but instead are based on the same concepts and methodology:

> A. So the publication is not a risk assessment, and the report becomes a risk assessment through this extended analysis and application of information around the concentrations presented in that report. And there is a bit of a -- there is a large distinguishing factor along those lines.
>
> Q. But with regard to the position that you're taking as to how to calculate the PDEs for NDMA and NDEA, isn't that set forth in this paper that was published in May of 2021?
>
> A. The mutation data, we had a conceptual total for the PDE calculation that we put forward, and some discussion points about how that could potentially change for a real risk assessment from there onwards. For the cancer-derived PDE where we did this off the BMDL lower, there's an extended version of this risk assessment, which I support, where you can do that calculation as well as calculating a BMD upper, so it wasn't complete in that respect. Also, the composite uncertainty factors were really for the global population, but for a smaller population, you can actually adjust these uncertainty factors, even for the cancer bioassay data, to reduce them from 500 to 50, which would cause an order of magnitude increase on the PDEs in my report. So there's -- this was more look at this, it can be done. Here's an example. This [paper] is not the finished product. My report is more this is how I am going to use this for a real assessment of risk in these patients.

[22] Johnson Report at 14-15; **Exhibit I**, 377:8 – 378:1, 479:5-22.

(**Exhibit M**, 216:6 - 217:19).

The point of Dr. Johnson's testimony was that the calculations in his paper are *conservative* when applied to the valsartan patient population, and that adjustments (such as for actual patient weight) could be made to answer more specialized questions like the general causation inquiry. No other paper had performed precisely the analysis undertaken by Dr. Johnson because he is the lead author of the first peer-reviewed article addressing this novel scientific issue that only arose in 2018. But the same methodology he utilized to calculate the PDEs for NDMA and NDEA were set forth in numerous other earlier publications.[23] Dr. Johnson applied reliable methodology to calculating the PDEs for NDMA and NDEA both in his report and *in his peer-reviewed publication on this same topic*, and it is neither surprising nor damaging to Dr. Johnson's opinions that such an analysis was not undertaken before the specific nitrosamine issue was known to the scientific community.

Plaintiffs further make unfounded assertions about Dr. Johnson's testimony regarding the co-authors of his 2021 paper. Dr. Johnson said nothing that remotely

[23] *See, e.g.*, Johnson Report at 56 & n. 140 (citing Müller L, Gocke E, Lavé T, Pfister T., *Ethyl methanesulfonate toxicity in Viracept--A comprehensive human risk assessment based on threshold data for genotoxicity*, TOXICOL. LETT. 190(3):317-329 (2009) (attached as **Exhibit O**)); Macgregor, *supra* n.4 (attached as **Exhibit E**); Johnson, *supra* n.4 (attached as **Exhibit F**).

"conceded industry bias," and as purported support for this Plaintiffs cite to testimony simply acknowledging the various professional affiliations of Dr. Johnson's co-authors.[24] All Dr. Johnson conceded was that *one possible interpretation* of Plaintiffs' loaded question was that pharmaceutical manufacturers would benefit from the establishment of higher permissible daily limits for NDMA and NDEA, but this testimony in no way demonstrates bias by Dr. Johnson or any of his co-authors in drafting the 2021 paper. On the contrary, Dr. Johnson's work in this area is regularly sponsored not just by the pharmaceutical industry but by global regulatory bodies and academic institutions. (Exh. C 100:10 – 101:7). That Plaintiffs cannot find more fertile ground in Dr. Johnson's testimony to support these claims of bias, instead pointing out meaningless exchanges such as Dr. Johnson not being aware that Glaxo-Smith Kline manufactures a specific brand name drug not at issue in this litigation,[25] underlines how specious the allegations are.

Finally, Plaintiffs latch onto the word "theoretical," used several places in Dr. Johnson's report, for the misguided and unsupported claim that "theoretical" data cannot serve as the basis for an expert opinion. First, Dr. Johnson's report explains precisely how "theoretical" dose response curves are accounted for in his analysis,[26]

[24] Motion at 15; **Exhibit M**, 218:24 – 223:12.

[25] Motion at 15-16.

[26] Johnson Report at 31-33.

and his citation to a peer-reviewed article for this proposition is no less authoritative simply because he is the article's lead author. Second, Plaintiffs cite to no authority for the proposition that "theoretical" data is somehow insufficiently scientific to be incorporated into an expert opinion.

E. Dr. Johnson's PDE calculation addresses the general causation question at issue – whether levels of impurities present in the valsartan medication increased the risk of cancer in patients, unlike the purpose of the FDA's conservative, regulatory-focused AI calculation.

Plaintiffs repeatedly misrepresent Dr. Johnson's testimony on his PDE calculation in a transparent attempt to cast a shadow on the underlying methods and calculations as novel or not generally accepted in the wider scientific community. However, the underlying methods and concepts which led to the PDE limits as stated in Dr. Johnson's expert report have been utilized in peer-reviewed studies long before this litigation. His application of well-established scientific principles to address the particular general causation question at issue – whether the NDMA and NDEA found by U.S. regulators in the valsartan medications pose a cancer risk to humans is precisely the risk assessment needed here. The decision of FDA and other regulatory agencies to set their AI levels using the conservative TD50 linear back extrapolation method demonstrates only that these regulators chose the quickest and most conservative measure to set the AI's while operating under a safety mandate. In the wake of determining this AI relied upon so heavily by plaintiffs, even FDA conceded as they must that the AI may be entirely meaningless as a risk assessment

if the body is already handling as much as 400 micrograms of endogenously produced NDMA, not to mention ordinary dietary intake.[27] The disparity between Dr. Johnson's PDE calculations and the AI levels set by regulators is due to these divergent purposes and the different scientific principles – with the PDE a much more precise human risk assessment as was explained by Dr. Johnson at length in his report and during his deposition:

> As one would assume from extrapolating back, a straight line from the TD50 and ignoring the dose-response relationship, you would assume that that would lead to a different value than if you accepted a nonlinear dose response with a DNA repair mechanism and carried that dose-response modeling to actually define the point of departure and extrapolate from that. And that would explain why you would see such a difference and the overconservative nature of a linear back-extrapolation approach compared to one based on nonlinearity.

(**Exhibit I**, 422:1-15).

The AI levels calculated by the FDA cannot serve as a proxy for the general causation inquiry in this litigation and certainly do not provide a basis to preclude Dr. Johnson's opinions. Dr. Johnson's PDE better accounts for the various factors ignored by the AI and directly addresses the question of whether there is an increased risk of cancer from taking valsartan to the actual valsartan patient population.

F. NDMA and NDEA display a threshold mechanism and are therefore appropriately assessed using the benchmark dose methodology for

[27] FDA, Nitrosamine Workshop – Report Final, at 14 (July 20, 2021), *available at* https://www.fda.gov/media/150932/download (last visited November 29, 2021) (attached as **Exhibit B**).

calculation of a PDE.

Dr. Johnson explained during his deposition that one of the assumptions – and an incorrect assumption as demonstrated in Dr. Johnson's report and testimony – underlying the FDA's decision to utilize the TD50 linear back extrapolation approach was that there was no established threshold mechanism for NDMA and NDEA.[28] While this misguided assumption led the FDA to use the TD50 rather than the PDE for purposes of setting the AI level, it does not indicate that the BMD approach to calculating a PDE is "not accepted." Plaintiffs also totally misstate the facts behind the AI in that FDA did not rely solely on *Peto* but took a harmonized TD50 value from the Lars database to make this quick and conservative calculation.

As discussed above, the methodology used by Dr. Johnson to calculate the PDEs for NDMA and NDEA using the BMDL approach are well-established. Though regulators may choose to use other methods for setting conservative regulatory standards, the principles of the method are widely accepted in performing the type of risk-based assessment at issue in the general causation phase of this litigation.[29] The fact that PDEs have not previously been calculated for NDMA and NDEA using the BMD approach is merely due to these compounds only drawing

[28] **Exhibit I**, 348:18 – 349:13.

[29] ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017), Note 4 (attached as **Exhibit G**).

significant research interest after they were unexpectedly discovered in the valsartan medication. By Plaintiffs' logic on this point, the FDA's AI levels would constitute a "new" or "novel" approach simply because these calculations had never before been published for these compounds in valsartan drug products. The BMD approach is an FDA-approved methodology for analyzing compounds like NDMA and NDEA that demonstrate a dose response threshold mechanism – which Dr. Johnson has shown is the case for both of these impurities.[30]

Finally, Plaintiffs argue that the fact Dr. Johnson's research in this area is ongoing means his conclusions based on nearly two decades of professional research and extensive publications are merely "investigational."[31] That Dr. Johnson continues to further his professional life's work through research into better quantifying the impact of O6-methylguanine-DNA methyltransferase ("MGMT") repair capabilities and assess its effect on the dose response threshold (which Dr. Johnson has already established exists) for compounds like NDMA simply emphasizes Dr. Johnson's deep expertise in this area and further undercuts

[30] *See* ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2017), Note 4 (attached as **Exhibit G**); FDA, M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (March 2018), (attached as **Exhibit H**).

[31] Motion at 19-20.

Plaintiffs' argument that his opinions are "litigation driven."

G. Dr. Johnson reasonably relies on the FDA-reported test results for purposes of analyzing the levels of impurities found in valsartan finished dose product.

The argument that Dr. Johnson "cherry-picked" his data by basing his calculations on the levels reported by the FDA inverts the cherry-picking inquiry.[32] It is Plaintiffs who attempt to ignore the most reliable, relevant testing data (which is the data reported by FDA, as explained by Dr. Johnson during his deposition). They argue instead that Dr. Johnson should have selectively relied on the highest outlier numbers from internal testing data, without regard to the consistency of testing methods used, whether that product was representative of the manufacturer's finished dose product as a whole, or whether the testing was performed on valsartan finished dose or valsartan API.

Contrary to Plaintiffs' allegations, Dr. Johnson specifically testified that he considered the manufacturers' internal testing data – and explained why such data was not the most reliable source of impurity levels – but nevertheless concluded that there was no increased risk of cancer to humans at levels an order of magnitude higher than even these highest-conceivable levels of exposure.[33] Dr. Johnson explained that the manufacturers' internal testing data did not show results using the

[32] Motion at 21-25.

[33] **Exhibit I**, 501:15 – 502:14.

same equipment for all products. The internal testing data covers both finished dose product and valsartan API, and despite Plaintiffs' attempt to simplify this issue there is significant uncertainty about how to translate the particular results of an API test to the levels which would be found in finished dose product manufactured using said API. Finally, the FDA has highly trained personnel with unparalleled access to the various manufacturers' internal data and processes, making the FDA-reported test results the most accurate proxy for levels actually present in valsartan medications sold in the United States.[34]

As an example of Plaintiffs' misguided attempt to critique Dr. Johnson's reliance on data from the same FDA that Plaintiffs dogmatically argue should be the final authority on calculating AI levels, Plaintiffs cite to internal testing produced by Torrent. (Motion Exh. P) First, the testing is of valsartan API, which Plaintiffs argue should be indistinguishable from testing of finished dose product despite ample evidence that these levels cannot be directly translated. Second, the median level reported for NDMA is 12.32 ppm, which is *less* than the level used by Dr. Johnson in assessing whether the levels of exposure exceed his PDE. (*See id.*) It would be inappropriate to selectively rely on only the highest test results reported by any manufacturer in trying to quantify the levels of impurities to which a Plaintiff might

[34] **Exhibit M**, 256:7 – 258:2.

reasonably have been exposed, and Dr. Johnson's decision not to do so here is scientifically sound and justified by his testimony.

Finally, Dr. Johnson's testimony that he has "seen no evidence of cancer being caused in humans within an order of magnitude higher than the PDE" is not unsupported. Rather it was explained in detail during the portion of Dr. Johnson's deposition testimony which Plaintiffs strategically chose not to present to the Court. Dr. Johnson's PDE calculation includes an uncertainty factor to account for the possibility that a given individual may have an MGMT deficiency. (**Exhibit I**, 485:6 – 486:22). This uncertainty factor allows a person with even a total deficiency in this area to fall within the calculated PDE. However, due to the rarity and lethality of such a deficiency, it is extremely unlikely there is any such individual in the age cohort of the valsartan patient population. Removing this uncertainty factor of 10, which would represent a PDE unadjusted for MGMT deficiency, increases the corresponding PDE values by a full order of magnitude.

H. Dr. Johnson's PDE calculations are based on robust scientific data for the proposition that certain levels of NDMA and/or NDEA will lead to no increased risk and no increase above background mutation rates.

Dr. Johnsons' conclusions that human DNA repair will account for and eliminate potentially harmful mutations at levels below his PDE are extensively supported by the literature cited in his report. Plaintiffs argue that the use of scientific

data studying nitrosamines cannot be applied to NDMA and NDEA, which ignores the fact that, as explained by Dr. Johnson, the adducts, mutations, and DNA repair pathways operate in the same manner.

Plaintiffs then demonstrate their continued misunderstanding of the PDE by arguing the Dr. Johnson's statement is that human DNA repair can eliminate "ALL" risk of genotoxic effects from NDMA. Rather, the PDE calculated by Dr. Johnson identifies the levels below which there is no increased risk for this patient population above the background mutation rates which is not accounted for by DNA repair.[35] Similarly, Plaintiffs point to the importance of MGMT expression in DNA repair mechanisms, and argue that Dr. Johnson has not attempted to quantify or account for variations in MGMT expression in calculating the PDE. But as pointed out above, Dr. Johnson's PDE includes a 10-fold uncertainty factor for MGMT expression, which accounts for all variation up to and including the all-but-impossible circumstance where a human survives to adulthood with a total MGMT deficiency. This adjustment and methodology, which Plaintiffs repeatedly misapprehend or ignore, are extensively documented.[36]

I. The dietary and occupational studies were considered and

[35] **Exhibit I**, 386:13-387:7.

[36] White, P.A., et al., *Quantitative Interpretation of Genetic Toxicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: Current Status and Emerging Priorities*, ENVIRONMENTAL AND MOLECULAR MUTAGENESIS 61:66-83 (2020) (attached as **Exhibit P**).

appropriately discounted for purposes of Dr. Johnson's analysis.

As a preliminary matter, Dr. Johnson did not agree that the dietary studies "showed a statistically increased risk of cancer."[37] This assertion is presented without any supporting citation, because it has none – Dr. Johnson merely testified he was aware of the existence of these studies.[38] To the extent any individual studies could be cherry-picked to argue in a single instance that there was some elevated risk from highly confounded exposure to nitrosamines through diet, Defendants' epidemiology experts (including Dr. Herman J. Gibb, whose opinions have not been challenged by Plaintiffs) have exhaustively addressed the inappropriateness of using these individual results to argue that they indicate an association between nitrosamines and cancer, much less a causal association.

Setting aside the misplaced epidemiological arguments, the dietary and occupational studies contain far too many uncontrolled variables to be useful for performing the type of risk assessment undertaken by Dr. Johnson. Dr. Johnson explained that he "considered those [dietary] studies and did not deem those human studies to be precise enough to be able to contribute to a human exposure limit calculation. In this instance, you would use an animal-based study, which is what I've done, as presented in my report." (**Exhibit I**, 427:17-24). Notably these same

[37] Motion at 27.

[38] **Exhibit I**, 425:7-16.

studies similarly have no bearing on and were not considered in establishing the AI levels which Plaintiffs' tout throughout their Motion.

Dr. Johnson is a toxicologist, and incorporating these highly confounded studies into his analysis would not aid the PDE calculation, which Plaintiffs would understand had they proffered an opinions from any toxicologist to support their theories in this litigation. The referenced dietary and occupational studies are at best the basis for an epidemiologist to review and begin to determine if an association or causal association exists – which is precisely the analysis that Dr. Gibb performed in his unchallenged report concluding the absence of any causal association. Neither the dietary studies nor the even more confounded occupational study in *Hidajat* contain information relevant to Dr. Johnson's toxicology analysis beyond providing general background on other potential sources of nitrosamines. The argument that the failure to somehow incorporate these studies, which Dr. Johnson nevertheless reviewed and considered, in his expert opinions is misplaced and does not serve as a basis to exclude or otherwise limit Dr. Johnson's testimony.

CONCLUSION

As Plaintiffs concede by failing to challenge his qualifications or fit, Dr. Johnson is uniquely qualified to opine on the general causation question and his PDE calculation will be helpful for the jury. Despite Plaintiffs' claims to the contrary, each of Dr. Johnson's opinions are well-supported by a reasoned and scientifically

appropriate methodology, drawing on his years of research and experience analyzing the impact of low-level impurities like the NDMA and NDEA at issue. Plaintiffs' Motion repeatedly mischaracterizes and misunderstands his report, his testimony, and his methodology, and offers no basis to exclude or limit any aspect of his opinions. For those reasons as described more fully in this response, Plaintiffs' Motion should be denied and Dr. Johnson's opinions should be admitted in their entirety.

Dated: December 1, 2021

Respectfully Submitted by the Defense Executive Committee on behalf of all Defendants,

By: */s/ Seth A. Goldberg*
Seth A. Goldberg, Esq.
Liaison Counsel for Defendants

DUANE MORRIS LLP
Seth A. Goldberg, *Liaison Counsel for Defendants*
Jessica Priselac, *Liaison Counsel for Defendants*
Lauren Appel
Coleen W. Hill
30 South 17th Street
Philadelphia, Pennsylvania 19103
Tel.: (215) 979-1000
Fax: (215) 979-1020
SAGoldberg@duanemorris.com
JPriselac@duanemorris.com
LAAppel@duanemorris.com
CWHill@duanemorris.com

Counsel for Zhejiang Huahai Pharmaceutical Co, Ltd., Huahai U.S., Inc., Prinston Pharmaceutical Inc., and Solco Healthcare US, LLC

Lori G. Cohen,
Victoria Davis Lockard
Steven M. Harkins
Terminus 200
3333 Piedmont Road, N.E.,
Suite 2500
Atlanta, Georgia 30305
(678) 553-2100
(678) 553-2386 (facsimile)
CohenL@gtlaw.com
LockardV@gtlaw.com
HarkinsS@gtlaw.com

Counsel for Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Actavis Pharma, Inc., and Actavis LLC

PIETRAGALLO GORDON ALFANO BOSICK & RASPANTI, LLP
Clem C. Trischler
Jason M. Reefer
Frank H. Stoy
38th Floor, One Oxford Centre
Pittsburgh, Pennsylvania 15219
Tel: (412) 263-2000
Fax: (412) 263-2001
CCT@PIETRAGALLO.com

Counsel for Mylan Laboratories, Ltd. and Mylan

Pharmaceuticals, Inc.

BARNES & THORNBURG LLP
Sarah E. Johnston, *Liaison Counsel for Retailer Defendants*
Kara Kapke
Kristen L. Richer
2029 Century Park East, Suite 300
Los Angeles, CA 90067
Tel: (310) 284-3798
Fax: (310) 284-3894
Sarah.Johnston@btlaw.com
Kara.Kapke@btlaw.com
Kristen.Richer@btlaw.com

Counsel for CVS Pharmacy, Inc. (incorrectly named as CVS Health Corporation)

ULMER & BERNE LLP
Jeffrey D. Geoppinger, *Liaison Counsel for Wholesaler Defendants*
600 Vine Street, Suite 2800
Cincinnati, OH 45202-2409
Tel.: (513) 698-5038
Fax: (513) 698-5039
jgeoppinger@ulmer.com

Counsel for AmerisourceBergen Corporation

DM1\12658314.1

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on December 1, 2021, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ Seth A. Goldberg
Seth A. Goldberg